DOCKET NO. 17224 CON(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of John Sefton	Group Art Unit: 1617
Serial No: 10/820,298	Confirmation No: 7456
Filed: April 7, 2004	Examiner: Badio, Barbara P
For: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS	

Honorable Commissioner of Patents and Trademarks
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Dear Sir:

This appeal is taken from the final rejection of all of the claims in an Examiner's action mailed May 20, 2005. Oral hearing is waived.

(1) REAL PARTY IN INTEREST

This patent application is assigned to Allergan, Inc, having its principal place of business at 2525 Dupont Drive, Irvine, CA 92612.

The application was originally assigned to Allergan Sales, Inc. via an assignment document recorded at Reel/Frame 011144/0193 on August 22, 2000.

Allergan Sales, Inc. (merged into Allergan Sales LLC 6/3/2002) assigned the application to Allergan, Inc. via an assignment document recorded at Reel/Frame 013898/0170 on April 7, 2003.

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(2) RELATED APPEALS AND INTERFERENCES

Notice of Appeal was filed in the parent case 09/367,712 on October 20, 2000. A new ground of rejection was issued in the Decision on Appeal by the Board on September 24, 2003. A second Notice of Appeal was filed (Appeal No. 2005-0938), which was decided in favor of Applicant on May 20, 2005.

(3) STATUS OF CLAIMS

Claims	Status
1-11	Rejected under 35 USC § 103 as being obvious

(4) STATUS OF AMENDMENTS

A response after final rejection was filed and considered, but not found persuasive by Examiner.

(5) SUMMARY OF THE INVENTION

The broadest claim at issue provides a method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid.

(6) ISSUES

Obviousness

The rejection of all claims under 35 USC 103(a) over Yamamoto ('906) and Nagpal ('279) in combination is the issue of this appeal.

(7) GROUPING OF CLAIMS

All claims stand or fall independently.

(8) ARGUMENT

OBVIOUSNESS

The claims are rejected as being obvious under 35 U.S.C. § 103 over Yamamoto ('906) and Nagpal ('279) in combination. In response to this, Applicant has provided evidence of unexpected results. If the Applicant correctly understand the Office Action's position, it disputes all of the Applicant's premises for asserting unexpected results except for one. These premises are listed below.

1) A general reduction of adverse events for the combination of tazarotene and a corticosteroid as compared to tazarotene alone is unexpected.
2) Combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone.
3) A general trend toward reduction in adverse events as corticosteroid potency is increased is unexpected.
4) There is a general trend toward reduction in adverse events as corticosteroid potency is increased.

Point 1 is an assertion of what a person of ordinary skill in the art would find unexpected. Point 2 is an assertion that Applicant's result was what a person of ordinary skill in the art would find unexpected according to point 1. Points 3 and 4 have a similar relationship. Point 3 does not appear to be disputed by the Office.

1. A general reduction of adverse events for the combination of tazarotene and a corticosteroid as compared to tazarotene alone is unexpected.

As a general principle, when a treatment with a therapeutically active agent is unchanged except that an additional therapeutically active agent is administered, an increase in side effects is expected. This assertion is supported by the affidavit, which says "[i]t is generally expected that administering two drugs to a patient will increase the adverse effects as compared to administering either of the individual drugs to the patient,

where the dose of the individual drug is the same for individual and combination therapy." This is not attorney argument, but the testimony of an expert. The Office Action contradicted the expert and asserted "[t]he general expectation with combination therapy is a reduction in adverse effect." The Office Action claims that "[t]he adverse effect of the active ingredients might be different," and thus a person of ordinary skill in the art "would not expect" an increase in adverse events for a combination.

Applicants agree that active agents might have different side effects. However, a combination of those two active agents would still be expected to have an increase in adverse events. Generally, adverse events are additive. For example, if active agent A has adverse effects M and N, and active agent B has adverse effects Y and Z, one would expect that combining them without changing the dose of either A or B would result in adverse effects M, N, Y, and Z. Thus, the combination has more adverse events (4) than the individual active agents (2 each). Because the adverse event contribution of each of the drugs in a combination may be different, the total number of adverse events is the most important quantity to be evaluated in terms of unexpected results. Furthermore, many adverse effects are common among many drugs, so common adverse effects may be expected to increase when combining drugs. The Office Action has provided no evidence that a person skilled in the art at the time the application was filed would have believed that the present combination would not have more adverse events than the individual components alone. By contrast, Applicant has provided expert testimony that the general rule in the art is that combining drugs ordinarily increases the adverse effects. Therefore, the evidence of record supports Applicant's assertion.

2. Combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone.

This assertion is also supported by the affidavit, which states "there appears to be a general trend that combinations of tazarotene and corticosteroids increase efficacy in the treatment of psoriasis while reducing the adverse events as compared to tazarotene alone." Again, the Office Action rejects the testimony of an expert, not attorney argument. The reason that the Office Action provided for not agreeing with this assertion is reproduced in its entirety below.

> Applicant also argues the data presented in Gollnick supports *the general trend of a reduction in adverse events with the combination of tazarotene and corticosteroids compared to tazarotene alone*. As stated in the previous Office Action, the *data shows no difference with the utilization of med- versus high-potency corticosteroid* and, thus, does not support the applicant's assertion of a trend towards a *decrease in adverse effect with increase in the potency of corticosteroid*. (Italics added.)

This reasoning does not even address the Applicant's assertion it was supposed to disprove. Note that the assertion of the Applicant in question is according to the Office Action that "the general trend of a reduction in adverse events with the combination of tazarotene and corticosteroids compared to tazarotene alone." However, the Office Action goes on to claim that the "data shows no difference with the utilization of med- versus high-potency corticosteroid." With all due respect, the comparison of medium to high potency corticosteroid is irrelevant to whether combining corticosteroids with tazarotene results in reduced side effects as compared to tazarotene alone. Thus, this does not disprove the Applicant's point. Finally, the conclusion drawn is not that adding a corticosteroid to tazarotene does not reduce adverse events, but that there is no "decrease in adverse effect with increase in potency of the corticosteroid." Thus, even if this conclusion could be drawn from that data (which the Applicant does not believe is the case), it is unrelated to the actual question that was supposed to be addressed, and the Office Action has failed to prove its point.

Not only has the Office Action failed to prove its point, but if one were to take the conclusion that there is no "decrease in adverse effect with increase in potency of the corticosteroid" as true, the Applicant's assertion is even easier to prove. If there is no trend toward a decrease in adverse events with increasing corticosteroid potency, then all of the corticosteroids have essentially the same effect regardless of potency. If all of the corticosteroids have the same effect regardless of potency, then all of the corticosteroids can be treated the same when comparing them to tazarotene alone to determine whether the combination has reduced adverse events. Averaging the adverse event profile of the corticosteroid combination groups yields the data shown below. The table shows that corticosteroids significantly reduce the erythema significantly, and the pruritus and irritation somewhat. More importantly, as explained above, the total number of adverse events is the most relevant to unexpected reduction of side effects, and the table shows an

undeniable reduction in the total number of adverse events for the combination treatment. Thus, if one accepts that there is no trend in reduction of adverse events with increasing corticosteroid potency, one is compelled to conclude that the combination reduces the total number of adverse events as compared to tazarotene alone.

	Pruritus	Erythema	Irritation	Burning	Total
No steroid	15	12	8	6	41
Steroid	14	6	6	5	32

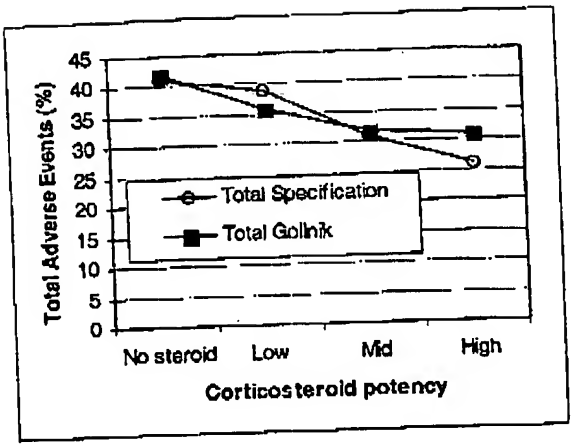
In conclusion, Applicant has presented an expert affidavit to support the assertion that combining a corticosteroid with tazarotene is associated with a general reduction of adverse events as compared to tazarotene alone. The Office Action disagrees with this but provides evidence and reasoning that does not even address the assertion of Applicant that it was supposed to disprove. Finally, even if the conclusion drawn in the Office Action were true (which Applicant does not believe), then this conclusion would further strengthen, not weaken, Applicant's position.

1. A general trend toward reduction in adverse events as corticosteroid potency is increased is unexpected.

This assertion is supported by affidavit, which says "[i]t is generally expected that increasing the potency of a corticosteroid will increase the adverse events." Since this is not challenged by the Office Action, Applicants assume that this statement is accepted as true.

2. There is a general trend toward reduction in adverse events as corticosteroid potency is increased.

	Total Adverse Events (%) Specification	Total Adverse Events (%) Gollnik
No steroid	41	42
Low	39	36
Mid	31	32
High	26	31



The table and plot above show both the data from the specification and the Gollnick reference. One does not need to be an expert to discern a trend. However, an expert has stated in the aforementioned affidavit that "there appears to be a trend of reduction in adverse events for the combination treatment of tazarotene and corticosteroid as the potency of the corticosteroid is increased." Further, Gollnick also states "there was a trend towards a lower incidence of treatment-related adverse events as corticosteroid potency increased." (p. 18, abstract, fifth line from bottom) Thus, two experts have observed the trend asserted by Applicants.

Once again, the Office Action disputes the experts, claiming that the data shows "no difference" between the adverse events of the mid- versus high potency corticosteroid. First, it is not even true that there is "no difference" between mid- and high potency corticosteroids. Although the difference between the mid- and high potency is not as great as some of the other comparisons, there is still a difference, particularly when viewed with the other data. It is not correct to draw a sweeping conclusion from the one pair of points which shows the least difference while ignoring the overwhelming weight of the data. As mentioned before, the total adverse events is the most important comparison for unexpected results in the present case, and the data clearly supports a trend of decreasing total adverse events with increasing corticosteroid potency.

The Office Action also claims that the data shows increase in burning in the taz/high group versus the other groups including the taz/plac group. It also shows an increase or no change in irritation in the taz/low versus the taz/plac group, similar incidence of erythema in all three groups given the corticosteroid; and an increase incidence of pruritus in taz/low group versus taz/plac group and an increase or no change in the taz/med group versus taz/plac.

Applicant points out that the fact that some data points are not consistent with a trend does not mean the trend does not exist. In fact, most real data contains outliers. The Office Action focuses on a few data points and ignores the overall picture. This is not a proper analysis of experimental data. Applicant again points to the table and plot of the total adverse events presented above. Surely the presence of a few outliers does not overcome the undeniable trend which is plainly discernable, and has been explicitly recognized by two experts in the affidavit and the Gollnik reference.

Applicants have presented four assertions which, if true, demonstrate that the claimed combinations have unexpected results. The Office Action has disputed three of these assertions. Each of these assertions has been supported by an expert affidavit, and the Office has disputed these assertions without providing any support which stands up to reasonable scrutiny. Therefore, Applicants have demonstrated unexpected results for the claimed combinations.

Concentration of the Corticosteroid

This and the previous Office Actions continue to assert that the appropriate comparison is the concentration of the corticosteroid compound in the composition, and not the potency.

> ...like the data presented in the present specification, the comparison [in the Gollnik reference] is with different doses of corticosteroids. Based upon the utilization of the low, of low, med-, and high-potency, the skilled artisan would have the reasonable expectation that the effective amount of each group would decrease accordingly and thus, comparison would be based on decreasing doses of corticosteroid with increase potency. However, it is noted that the amount of high potency corticosteroid is twice the amount of med-potency corticosteroid in the present specification or for times the amount of low-potency corticosteroid in Gollnick reference.

As Applicant pointed out in previous responses, the appropriate comparison made by those skilled in the art is the potency of a corticosteroid formulation, not the concentration of the corticosteroid compounds. The reason the specification and the Gollnik reference compare results by potency is because that is the meter used in the art used to rank the efficacy and side effect profile of corticosteroid formulations. This method has been sanctioned by Applicant, Gollnik, and presumably the peer reviewers of the *British Journal of Dermatology*, the journal that published the Gollnik article. The Office Action has provided no evidence other than the unsupported opinion of the Examiner, that this is not a proper method. In the DECISION ON APPEAL of parent case Application No. 09/367,712, the Board also sanctioned Applicant's position on this issue. The relevant parts of that decision are reproduced below.

> **As we understand the examiner's assertion (Answer, p. 5), the evidence of record does not provide a "true side-by-side comparison" of the reagents because different concentrations of corticosteroids were used.** More specifically, in the Final Office Action, the examiner points out (bridging paragraph, pages 2-3), "Example 1 and the Figures compare alternative topical application of 0.1% tazarotene gel and a placebo, 1% hydrocortisone acetate (low-potency corticosteroid), 0.05% alcometasone dipropionate (medium-potency corticosteroid) or 0.1% betamethasone valerate (high-potency corticosteroid)." According to the examiner (Final Office Action, page 3), "in order to argue unexpected and/or unobvious results, the amount of corticosteroid in each case has to be kept constant.
>
> However, as appellant points out (Brief, page 5), since the potencies of the corticosteroids differ, a "comparison of a concentration of one compound to a concentration of a different compound is not proper." Rather, as we understand appellant's argument (Brief, page 6), the use of different concentrations of each corticosteroid effectively "normalizes" the corticosteroids relative to their potency. According to appellant (id.),
>
> > The potency of the corticosteroid is assigned according to the particular formulation in which it is contained. Thus, the 1% hydrocortisone acetate formulation used in the patent specification is considered to be low-potency at a concentration of 1% in the vehicle it is administered. The same is true for 0.05% alcometasone dipropionate being a medium-potency corticosteroid and 0.1% betamethasone valerate being a high-potency corticosteroid.

According to appellant (id.), "[t]he whole point of assigning potency to a corticosteroid formulation is to indicate the activity of that formulation, and thus treatment for a particular condition is determined according to the assigned potencies of the various corticosteroid formulations." In support of this assertion appellant relies on Cornell (et. al. "Correlation of the Vasoconstriction Assay and Clinical Activity in Psoriasis," Arch Dermatol, Vol. 121, pp. 63-67). The examiner, however, fails to address appellant's argument or the Cornell reference, maintaining instead (Answer, page 5),

> [t]he examiner sees no reason why applicant could not utilize similar amounts of corticosteroids in each case. In addition, the utilization of low-, mid- and high-potency would imply that at identical concentrations, the efficacy of corticosteroids would be as recited and, thus, the skilled artisan would expect the high-potency corticosteroid to be most effective when used at similar concentration as the others.

The examiner, however, appears to miss the point. As the examiner recognizes the concentration of high-potency corticosteroid used in the experiments was 10-fold less than the concentration of low-potency corticosteroid. As appellant points out (Brief, page 6), the

> [e]xaminer's position is inconsistent with itself in that [e]xaminer alleges "[t]he skilled artisan would have the reasonable expectation that the higher concentration of betamethasone valerate [(a high-potency corticosteroid)] would result in better improvement over treatment with lower concentrations of alcometasone dipropionate [a medium-potency corticosteroid)]" but fails to recognize that the same reasoning would lead a skilled artisan to expect that the lower concentrations of alcometasone dipropionate [(a medium potency corticosteroid)] and betamethasone valerate [(a high-potency corticosteroid)] relative to hydrocortisone acetate [(a low-potency corticosteroid)] would result in the treatment by the former two compounds being less effective. If the former two treatments are expected to be less effective, then the significant improvement of betamethasone valerate [(a high-potency corticosteroid)] over hydrocortisone acetate [(a low-potency corticosteroid)] that was observed must be unexpected.

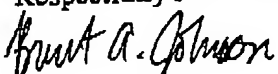
Accordingly, **we are not persuaded by the examiner's unsupported assertion regarding appellant's evidence.** (footnotes omitted, full Cornell cite added, emphasis added)

Since the Board has already endorsed the Applicant's position on the issue of concentration. Applicant submits that the rejection on this ground is not proper.

In summary, the Office Actions have failed to provide any reasonable ground for rejecting Applicant's showing of unexpected results, and removal of the obviousness rejection is proper.

In view of the above, the Board is asked to reverse the Examiner's holding of all of the pending claims as unpatentable and direct the Examiner to pass the claims to issue.

Respectfully submitted,



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(7) APPENDIX

CLAIMS

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a corticosteroid.

2. The method of claim 1 wherein said corticosteroid is selected from the group consisting of fluocinolone acetonide, mometasone furoate, fluocinonide, diflorasone diacetate, fluticasone propionate, betamethasone dipropionate, clobetasol propionate, and betamethasone valerate.

3. The method of claim 1 wherein tazarotene is applied as a 0.1% gel.

4. The method of claim 1 wherein said corticosteroid is ~~a~~ selected from the group consisting of mometasone furoate, fluocinonide, alclometasone dipropionate, and betamethasone valerate.

5. The method of claim 4 wherein said corticosteroid is selected from the group consisting of alclometasone dipropionate, and betamethasone valerate.

6. A method for treating psoriasis in a human subject by topically applying to the psoriatic skin of said subject an effective amount of tazarotene and an effective amount of a corticosteroid.

7. The method of claim 6 wherein tazarotene is applied as a 0.1% gel.

8. The method of claim 7 wherein said corticosteroid is a cream.

9. The method of claim 8 wherein said corticosteroid is selected from the group consisting of mometasone furoate, fluocinonide, alclometasone dipropionate, and betamethasone valerate.

10. The method of claim 9 wherein said corticosteroid is selected from the group consisting of alclometasone dipropionate, and betamethasone valerate.

11. The method of claim 6 wherein tazarotene is administered once daily in the evening and the corticosteroid is administered once daily in the morning.